Bandolier 152

Independent evidence-based thinking about health care

On inevitability

Bandolier should occasionally leave this space deliberately blank, as an invitation for readers to write their own editorial comments. Nothing profound, perhaps, and nothing profound needed. Rising to profundity is a rare skill, only rarely used. Look at any book of quotations and see how few are quoted more than once, and meditate on how few people ever get a mention.

One wonders whether those of us consigned to the unquoted of history are just stunned by seeing lessons being re-learned, and mistakes being re-made. Bandolier was moved by an electrician taking out every other light bulb to save on electricity, a solution from high power management consultants to financial problems. Fourth time round on that one.

It's the same wherever you look. This issue of Bandolier will have readers seeing examples of lack of good evidence of effect, or good evidence of lack of effect, of sensible combining of data, and the not so sensible. But, hey, let's not get overly worried that this is a sign of great age, but rather the benefits of experience and wisdom. We still may not be able to make bricks without straw, but at least we don't waste time trying.

Great age and wisdom, if they do come together, are said to bring the realisation of the inevitability of failure. Yet any quality control expert, or any thoughtful person working in manufacturing, or building, or anywhere, will know that things ***will*** go wrong. It is also true in computer security, and for those interested there is fun review on the US NSA website (www.jya.com/paperF1.htm).

Tucked away in this issue of Bandolier are some inevitability themes: the inevitability that complementary therapies either have evidence that they are not effective or no evidence that they are, and that things go wrong sometimes, even with those things we take for granted.

In this issue

PPIs for reflux oesophagitis

When estimating relative efficacy of different treatments in meta-analyses of randomised trials, the usual situation is that we have many comparisons with, typically, placebo, but few direct comparisons between treatments. As a consequence of this we resort to indirect efficacy. It is a bit like testing every athlete for how long it takes them to run 100 metres individually (indirect comparison = world record) as opposed to who is fastest in a single race (direct comparison = Olympic champion).

It is unusual to have a feast of large, good quality, direct comparisons, but that is the situation in a meta-analysis of proton pump inhibitors (PPI) for healing of reflux oesophagitis [1]. This sort of data can help us generate information on relative efficacy in order to help formulate cost-effective strategies.

Systematic review

The systematic review built on an earlier one, with wide searching up to early 2005 for randomised trials comparing PPIs with esomeprazole. Trials chosen were those of European licensed standard doses of a PPI with esomeprazole 40 mg.

The outcome of interest was endoscopic healing data at four and eight weeks, in patients with comparable grades of oesophagitis (Los Angeles A-D or equivalent). Where necessary data from trials was recalculated with the number of patients randomised, to ensure a consistent intention to treat approach.

Results

Eight trials were identified, with 14,800 patients. Of these about 7,400 used esomeprazole 40 mg, 3,300 lanzoprazole 30 mg, 2,400 omeprazole 20 mg, and 1,700 pantoprazole 40 mg. No trials were identified with rabeprazole. Trials generally examined patients with grades A-D oesophagitis, though two limited patients to grades B and C or C and D.

The main results calculated from data in the paper are shown in Table 1. Esomeprazole 40 mg was significantly better than other PPIs used in these trials, with higher healing rates at four and eight weeks (Figure 1).

Analysis by baseline Los Angeles classification showed that, at eight and four weeks, healing rates tended to be lower at higher initial grade. Thus four week healing rates for esomeprazole 40 mg ranged from about 82% for grade

A to about 50% for grade D. Eight week healing rates for esomeprazole 40 mg ranged from about 92% for grade A to about 77% for grade D. Similar but lower results were reported for the other PPIs combined.

Comment

The first thing to bear in mind is that two of the three authors of the meta-analysis were employees of the manufacturers of esomeprazole. That is not necessarily a bad thing, but the thrust of the analysis, with esomeprazole 40 mg as the common comparator which had to be in an included trial, would tend to exclude other trials and limit the evidence we have to look at.

A different approach, which might be interesting, would be to compare relative efficacy using placebo, and using esomeprazole or other common comparators to see if they give the same order of efficacy. Such an approach might also include non-standard or non-licensed doses, further broadening the available evidence if there were sufficiently large amounts of data in properly conducted trials with the same outcomes and conducted in patients with similar initial disease severity. A case for an extended systematic review, probably.

A second observation from looking at the individual trials is how consistent the results were. Figure 2 shows the eight week healing rates in the esomeprazole arms of the eight trials. With high event rates and large numbers of patients, the result of each trial is close to the overall average of 88%. This is quite unlike the situation of small numbers and low event rates.

A third moment for reflection is for the economic consequences of small differences between healing rates. The immediate thought on costs would be to leap to the lowest acquisition cost, in this case generic omeprazole 20 mg, at about £13 for four weeks treatment, rather than somewhat more effective, but expensive, branded PPIs that cost up to twice as much.

It all depends on the cost of someone not healed. As that increases, the economics change, so a good health economic analysis would help in decision-making.

Figure 1: Percentage of patients with endoscopic healing of reflux oesophagitis for four common PPI doses

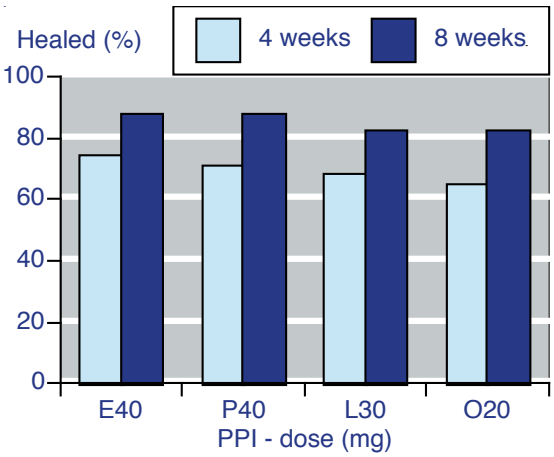
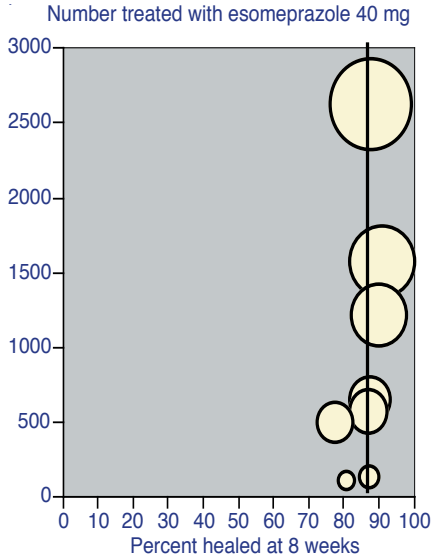


Figure 2: Eight week healing rates for esomeprazole 40 mg in individual trials



Reference:

1 SJ Edwards et al. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis – a comparisons of esomeprazole and other PPIs. Alimentary Pharmacology & Therapeutics 2006 24: 743-750.

Table 1: Comparison of esomeprazole 40 mg daily with other PPIs in endoscopic healing of reflux oesophagitis after four and eight weeks of treatment

Comparator	Number of		Percent healed with		Relative benefit (95% CI)	NNT (95% CI)
	Trials	Patients	Esomeprazole 40 mg	Comparator		
At 4 weeks						
Lanzoprazole 30 mg	3	6526	73	68	1.07 (1.04 to 1.10)	22 (15 to 42)
Omeprazole 20 mg	3	4877	74	65	1.14 (1.10 to 1.18)	11 (8.6 to 15)
Pantoprazole 40 mg	2	3397	77	71	1.09 (1.04 to 1.13)	16 (11 to 32)
At 8 weeks						
Lanzoprazole 30 mg	3	6526	86	83	1.04 (1.02 to 1.06)	30 (20 to 65)
Omeprazole 20 mg	3	4877	89	82	1.08 (1.06 to 1.11)	16 (12 to 23)
Pantoprazole 40 mg	2	3397	90	88	1.02 (1.00 to 1.04)	49 (24 to infinity)

A QUESTION OF STOCKINGS

How long should your stockings be? Not a frivolous question this, but a serious issue about whether graduated compression stockings should be thigh length, or whether we can get away with stockings just up to the knee to prevent deep venous thrombosis (DVT). A somewhat difficult (either confused, or confusing, depending on point of view) systematic review [1] provides some evidence, and a lesson in when not to combine dissimilar data.

Systematic review

It looked for randomised trials on the use of knee versus thigh length graduated compression stockings for thromboprophylaxis in surgical patients, and the use of knee length stockings versus no stockings in long haul flight passengers. The trials had to use objective tests for deep venous thrombosis interpreted blind to allocation and with predefined criteria for an abnormal test, and investigate DVT above or below the knee.

Results

In surgical patients, five trials with 592 patients showed no difference between knee and thigh length stockings (Figure 1, Table 1). As Figure 1 shows, the individual trials had widely varying event rates. In different trial arms the percentage of DVTs ranged from 2% to 65%. We don't know very much about these patients, except that in three trials they underwent general surgery, and in two they were orthopaedic patients (two small trials with higher event rates).

In long haul flight individuals the effect of using knee length graduated compression stockings was considerable (Figure 2, Table 1). Only 0.2% of people using stockings had a DVT, compared with 3.7% in those without stockings. This was a highly significant reduction in risk, corresponding to a number needed to treat with knee length graduated compression stockings of 28 (95% CI 21 to 42) to prevent a DVT in one of them. Again, we are told nothing about these participants without reading the original trials.

Comment

What can we make of all this? Bandolier would make no hard judgements without a more detailed look at the evidence because of obvious inconsistencies and mistakes in the paper. For knee versus thigh length graduated compression stockings the lack of a statistically significant result in this limited trial set probably rules out any large difference, but does not exclude a small one. Whether a small difference would be clinically significant or overcome any practical or cost differences depends on circumstances.

The reduction in DVT incidence compared with no stockings comes from a larger data set, and with a big effect. For people at higher risk on longer flights, it certainly makes the use of these stockings worth considering. It would be better if we knew the exact definition of higher risk, so we could judge for ourselves.

Figure 1: Individual trials in surgical patients

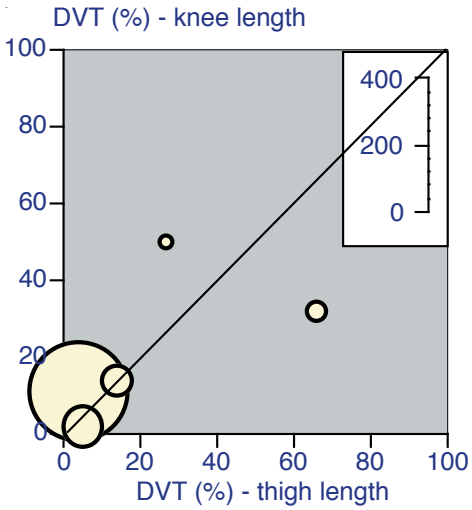


Figure 2: Individual trials in long haul flight passengers

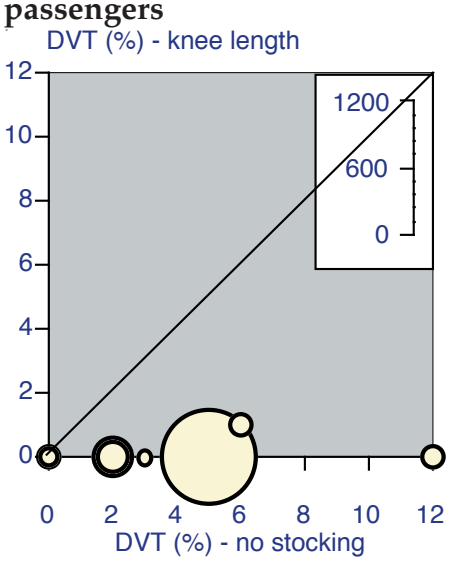


Table 1: Results of a comparison of knee length graduated compression stockings versus thigh length stockings in surgical patients using, versus no stockings in long haul flight passengers

Patient group	Number of		DVT (%) with		Relative risk (95% CI)
	Trials	Patients	Knee	Control	
Surgical patients	5	592	14	13	1.1 (0.7 to 1.6)
Long haul flight passengers	9	2482	0.2	3.7	0.1 (0.05 to 0.26)

In surgical patients, control was thigh length compression stockings. In long haul passengers, the control was no stockings

Reference:

1 MS Sajid et al. Knee versus thigh length graduated compression stockings for prevention of deep venous thrombosis: a systematic review. European Journal of Endovascular Surgery 2006: doi:10.1016/j.ejvs.2006.06.012

Risk and obstetric epidurals

I doubt if any of us would ever feel the same confidence about safety as JE Salk, who, when questioned about the safety of his polio vaccine, is reputed to have replied "*It is safe, and you can't get safer than safe*". The trouble with this concept of safe is that we know that some bad thing is likely to happen at some time, even if it is an extremely remote possibility. And if you multiply remote risk by many people, then some finite numbers are bound to pop up. And if the numbers have very dire consequences attached to them, the notion of safe tends to go out of the window.

Epidurals are routinely given during childbirth, to as many as 2.4 million US women every year. A new systematic review [1] of observational studies affords an insight into the safety of this procedure.

Systematic review

The basis of the review was an extensive search for observational studies regarding adverse events associated with epidural catheter use, not limited to obstetrics. The search included electronic searches, hand searching of major anaesthetic journals, reference lists, and reviews. Studies with fewer than 200 patients were not sought, as they were unlikely to report on rare events, and case reports would be unlikely to have a denominator to calculate rate.

Outcomes of interest were epidural haematoma, infection, and neurological injury in the shorter (less than one year) and longer term. There were various planned sensitivity analyses, including larger and smaller studies, and more and less recent studies.

Results

In all, 27 observational studies reported on 1.37 million women. Only five studies were identified initially through electronic searches, with most (20) identified through reference lists. Larger studies with more than 10,000 women per study tended to have been published since 1990, and smaller studies tended to have been published before 1990.

Not all studies reported on all outcomes, so the number of patients varied somewhat. The main results were:

- Epidural haematoma occurred in six women, at a rate of about 1 in 170,000 in larger, more recent studies.
- Deep epidural infection occurred in 11 women in total, at a rate of about 1 in 145,000 women in larger, more recent studies.
- Persistent (more than one year) neurological injury occurred in three women, at a rate of about 1 in 240,000 women in larger, more recent studies.

Transient (less than one year) neurological injury occurred in 288 women in total, at a rate of about 1 in 6,000 in larger, more recent studies. In individual studies the risk of transient neurological injury varied between about 1 in 100 to more than 1 in a million (Figure 1), though larger studies tended to be more consistent.

Comment

Many issues are highlighted by a study like this. Foremost is that of causation. While we are used to thinking that childbirth is safe, there are reports of spontaneous occurrence of epidural haematoma, deep epidural infection, and neurological problems with childbirth when epidurals have not been used. So while these outcomes may be related to the use of the epidural, we don't know this for sure.

Another is the need for very large numbers to estimate risk accurately. Even with the largest data set, for transient neurological injury, the degree of variability seen in Figure

Figure 1: Individual studies, showing the event rate and the individual risk for a woman for transient neurological injury following obstetric epidural

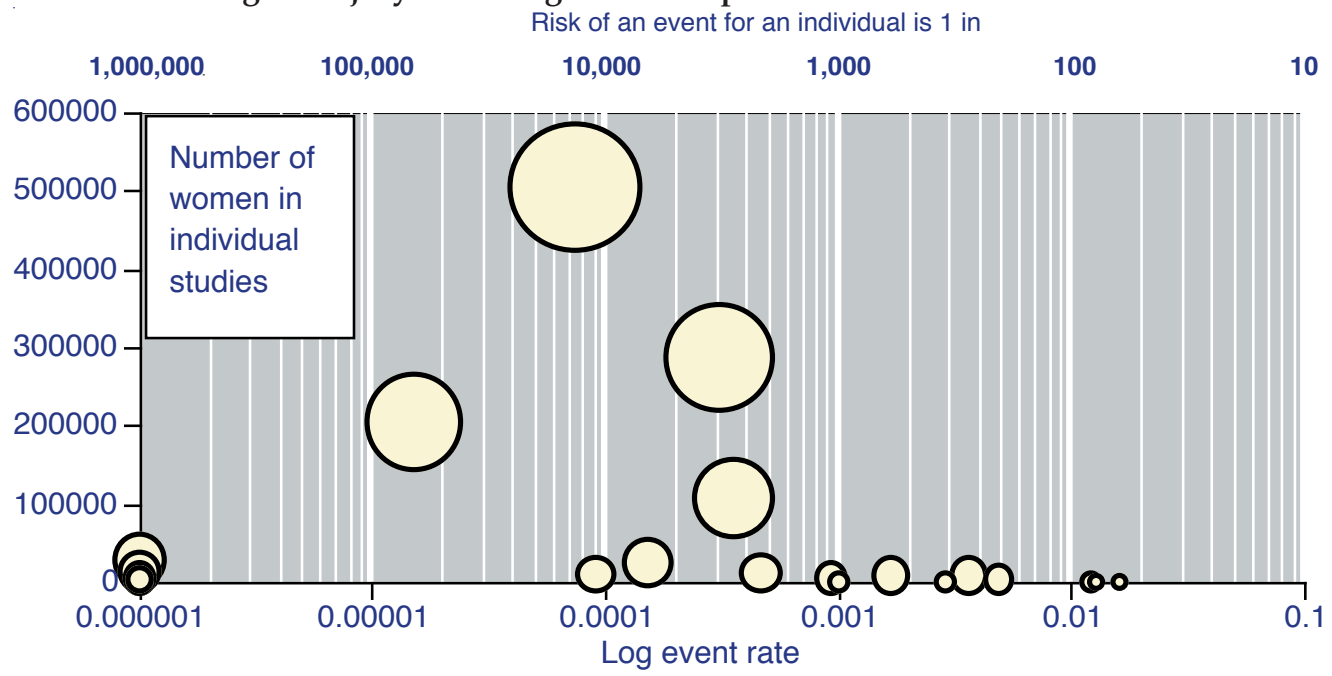
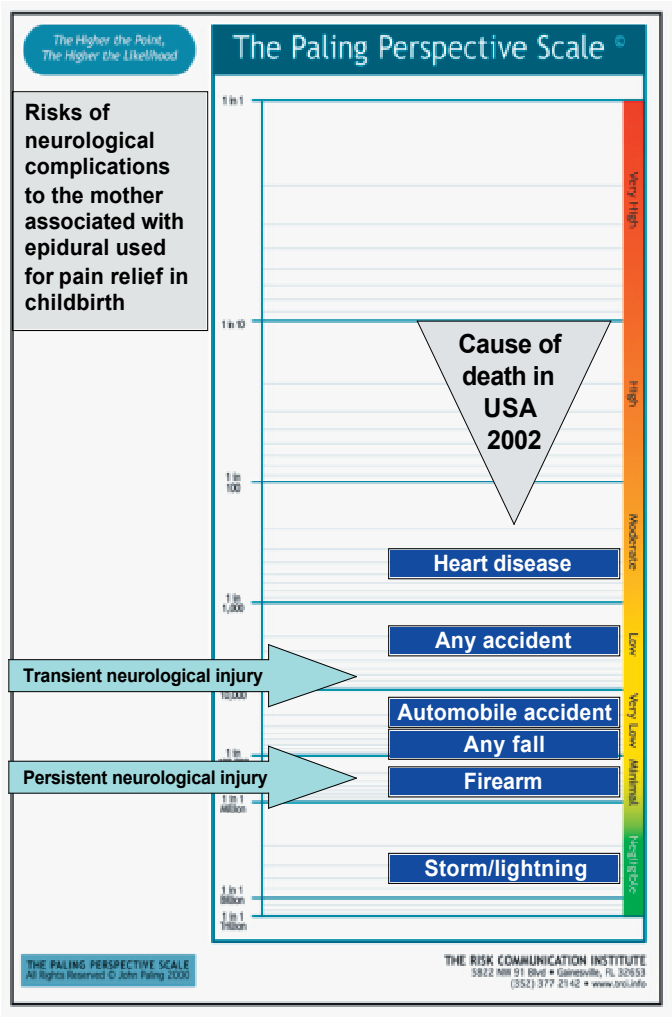


Figure 2: Risk of neurological injury shown in a Paling Perspective Scale



1 was profound. Even with large numbers in the denominator, our estimate of the actual rate will be less than accurate, but the best we can do with what we have. A related point is the need to perform sensitivity analysis using larger, better, studies.

We can try and put the risks into the Paling Perspective Scale (Figure 2). There are two difficulties with this. We know only about the duration of these neurological injuries, not their severity. They are certainly not deaths, which is why this particular version of the Paling Scale may be misleading, other than tell us about the rate of event. We need relevant comparisons for these sorts of injuries.

Finally, though, what can we say about safety of epidurals used during childbirth? It is often said that adverse events are under-reported. Yet here the review has accumulated large numbers of women in larger, more recent, studies, where the importance of complete reporting was known. These results are probably a fair reflection of the real world.

Reference:

1 W Ruppen et al. Incidence of epidural hematoma, infection, and neurological injury in obstetric patients with epidural analgesia/anesthesia. Anesthesiology 2006 105: 394-399.

How long do pathogens persist on surfaces?

So what's the answer? Given the major interest in hospital acquired infections, one might expect large amounts of useful information presented in a straightforward way, in order that we can organise services to minimise risk to professionals and patients. A systematic review [1] implies that our knowledge is limited.

Systematic review

The review set out to find articles in PubMed relating to survival of pathogens on surfaces using a broad strategy, and following up on any useful citations in studies that had been found, supplemented by checking textbooks on infection control and microbiology. Any report was included, and the range of duration abstracted.

Results

Many reports were found, and there are 126 references, a useful source for others wanting more detailed information. For most pathogens there were only a few citations. The larger the number of citations, the wider the range of persistence.

For bacteria, for example, the range for E coli (11 references) was 1.5 hours to 16 months, and for S aureus, including MRSA (six references), between seven days and seven months. For clinically relevant fungi, the range was up to four months, and for viruses days to months.

Comment

Not the answer to everything, but possibly the only answers that are available. It seemed to be the case that, as one might expect, low temperatures and higher humidity increased persistence. It seems that, whatever the actual answer, persistence of nosocomial pathogens on surfaces is sufficiently long to become a continuous source of transmission in the absence of effective preventive surface disinfection. Keep cleaning effectively is the message that is being heavily reinforced here.

Of course, it is all more complex than this when it comes to hospital acquired infections and the damage they do to individuals and hospitals. The arguments appear to have been simplified to handwashing, and while that is important, along with cleaning surfaces, an effective response will come from a number of different actions combining to reduce the problem. Reading this paper is a start because it helps show one element of this huge problem.

Reference:

1 A Kramer et al. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infectious Diseases 2006 6:130 (www.biomedcentral.com/1471-2334/6/130).

The trouble with aspirin

Bandolier is always interested to revisit a topic when some new evidence, new analysis, or new thoughts make it relevant. Low dose aspirin (LDA) is an important topic, and worth revisiting for a new look at the data.

We know that it does good in people at high cardiovascular risk. We also know that it does some harm in a variety of ways. A new meta-analysis [1] provides a better insight into some of the harm.

Systematic review

This followed a fairly standard path of searching, and was able to draw on many previous meta-analyses in this therapeutic area. Studies for inclusion were those comparing aspirin with placebo for primary or secondary prevention, or prophylaxis of deep venous thrombosis. Aspirin had to be low dose (75 to 325 mg daily).

Studies had to provide information on bleeding events, non-cardiovascular deaths, or discontinuations or symptoms for other than bleeding or cardiovascular events. They had to be randomised, have a duration of two months or longer, and have 100 patients or more in each treatment arm.

A series of outcomes were extracted from the trials, but the outcomes of primary interest were any major bleeding, major gastrointestinal bleeding, and intracranial bleeding. When not otherwise described as major, those needing transfusion were so defined.

Results

The basis of the analysis was 14 randomised trials with 57,000 participants, about 53,000 of whom were in studies lasting 12 months or longer. Annualised event rates for the three primary outcomes, with calculated numbers needed to harm for LDA compared with placebo, are shown in Table 1. Those taking LDA have an additional risk of any major bleed or major gastrointestinal bleed of about one person in 800 every year.

Comment

In longer-term trials in people at high risk of cardiovascular problems (previous heart attack, stroke, or other high risk causes), there are clear benefits from using LDA in reducing fatal or nonfatal heart attacks or strokes, or vascular deaths. Table 2 shows the benefits for LDA and placebo in high risk patients in an annualised form calculated from the Antithrombotic Trialists' Collaboration (Bandolier 108), alongside the annual risks of all major bleeding events.

Benefits outweigh the risks, though there are probably other risks, so this will overstate the benefit:risk balance. It is possible to present the information in a number of ways, both as a percentage rate, or as a risk or odds, and for the actual rates or the difference.

In people who do not have high levels of cardiovascular risk, the benefits will fall, but the potential for gastrointestinal bleeding almost certainly remains the same. And yet our newspapers, and the tone of the media in general, is that taking a small amount of aspirin every day is beneficial for everyone. Not stated, but implied, is that it harms no one. It might be a useful example to use when explaining that all drugs are also poisons, and that safety is relative. For high risk patients the balance is easy to remember: good outcome 1 in 70, bad outcome 1 in 770.

Reference:
1 KR McQuaid, L Laine. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. American Journal of Medicine 2006 119: 624-638.

Table 1: Meta-analysis of bleeding events in about 57,000 patients taking low dose aspirin, showing the absolute annual event rates with low dose aspirin (LDA) and placebo, and relative risk and number needed to harm

Bleeding event	Annual event rate (%) with LDA	Annual event rate (%) with Placebo	Relative risk (95% CI)	NNH (95% CI)
Any major bleeding	0.31	0.18	1.7 (1.4 to 2.1)	769 (500 to 1200)
Major gastrointestinal bleeding	0.24	0.12	2.1 (1.6 to 2.7)	833 (530 to 1400)
Intracranial bleeding	0.08	0.05	1.7 (1.1 to 2.4)	3300 (1250 to 10,000)

Table 2: Some calculations on the annual benefits and harms with placebo and low dose aspirin (LDA), and the risk difference to demonstrate additional annual risk

Event	Annual rate with placebo		Annual rate with LDA		Annual rate difference	
	Percent	Risk	Percent	Risk	Percent	Risk
Fatal or non-fatal heart attack or stroke, or vascular death	**6.9**	**1 in 14**	**5.6**	**1 in 18**	**1.4**	**1 in 71 will benefit**
Fatal or non-fatal major bleeding event	0.18	1 in 560	0.31	1 in 320	0.13	1 in 770 harmed

Electromagnetic energy for knee osteoarthritis

The pages of our newspapers offer all sorts of quackery for all sorts of medical conditions. One suggested treatment is pulsed electromagnetic field therapy, in which magnetic fields are pulsed on and off to supposedly promote tissue healing, to relieve pain, and inflammation. Some reviews have been produced, with equivocal results, perhaps due in part to the variable quality of trials included. A new systematic review [1] provides a clearer picture.

Systematic review

The review used a Cochrane search strategy to find randomised trials of pulsed electromagnetic field therapy in adults with knee osteoarthritis who had clinical or radiological diagnosis. Any type of pulsed electromagnetic field therapy was accepted, using validated patient-reported pain and function as the outcomes.

Results

Five studies with 276 patients met the inclusion criteria. They had good reporting quality, all scoring 3 out of 5 points or better on a standard scale. Duration of treatment was two to six weeks, with two using a visual analogue scale for pain, and three using the WOMAC scale.

All five trials reported pain outcomes (Figure 1). No single trial showed any benefit of pulsed electromagnetic field therapy over placebo for pain, nor was there any difference overall. Four trials measured function. One showed a trivial improvement, but there was no improvement overall.

Comment

Despite the small number of small trials, there was not a smidgen of clinical benefit. It is good, though, that people have taken the trouble to test pulsed electromagnetic field therapy in properly randomised trials.

Reference:
1 CJ McCarthy et al. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: a systematic review. BMC Musculoskeletal Disorders 2006 7:51 (www.biomedcental.com/1471-2474/7/51).

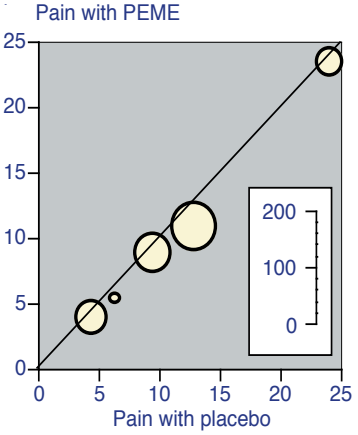


Figure 1: Individual trial results of pulsed electromagnetic energy (PEME) compared with placebo, showing actual pain scores on whatever scale used

Hypnotherapy for IBS?

Irritable bowel syndrome (IBS) is common, with each UK GP seeing an average of about eight patients every week. It is unpleasant for sufferers, negatively affects quality of life, and is expensive for health services. A large proportion of patients do not do well with conventional therapy, and many seek unconventional alternatives.

One of these is a form of hypnotherapy known as gut-directed hypnotherapy. It is based on relaxation to try to normalise gut function. Because there are claims that it works, some purchasers are tempted to provide a service. A systematic review of trials [1] suggests a large degree of caution is warranted.

Systematic review

Authors sought studies, of any design, in nine electronic databases, and even contacted authors for information about any further studies.

Results

Eighteen unique studies were identified and included in the review, four randomised trials, two controlled trials, and 12 uncontrolled studies. All concluded that hypnotherapy had some beneficial effect.

The four randomised trials studied 153 patients. They used five to 12 gut directed hypnotherapy sessions in patients who were mostly refractory to conventional therapy. Controls tended to receive usual monitoring, though one trial used supportive psychotherapy. About half the patients were in trials of 12 weeks, and the remainder in one trial with 12 months follow up.

Three smaller studies indicated some significant statistical improvement, usually in symptom scores at 12 weeks. The largest trial with the highest quality score indicated that differences were not maintained at six months.

Mind over bowel?

It sounds familiar. This is exactly what we find in so many reviews of unconventional therapy. By now we should have learned the lesson, that without good evidence hope is likely to be trumped by later experience.

The authors conclude, rightly, that there is far too little evidence to justify use of hypnotherapy in any circumstance. At least one good quality, large trial, with long follow up should be the absolute minimum requirement for efficacy, but would still be less than what we expect for medicines, where two positive trials are needed. Don't hold your breath.

Reference:
1 S Wilson et al. Systematic review: the effectiveness of hypnotherapy in the management of irritable bowel syndrome. Alimentary Pharmacology and Therapeutics 2006 24: 769-780.

Book review

Imogen Evans, Hazel Thornton, Iain Chalmers. Testing treatments – better research for better healthcare. The British Library. 2006. ISBN 0-712-3-4909-X. 116 pp; Cost £12.95.

An awful lot of people are going to get cross when they start reading this book, but they should persevere, because they will end up agreeing with its most important thesis.

The start would not appear in any anthology of strategies on how to win friends and influence people. The stark message seems to be that medicine is crap, doctors and pharmaceutical companies are to blame, and the rest of us are spinelessly complicit in letting it happen. None of which is softened by some 1980s anecdotes from Nick Ross, an ex TV presenter. The first few chapters will have you screaming at the book much as you would when listening to a government lickspittle on TV telling why the NHS is better now than it ever has been. Yes, but…. will utter from your lips time and again.

You will feel, with some justification, that many criticisms are unfair, in large part because they are commonly known examples from medical history. Things that happened in the 1950s, or 60s, or even 90s may be recent in a common historical context, but the pace of change in medicine has been so rapid that they could be regarded as Jurassic. Bandolier well remembers pointing out Sir Hans Krebs (yes, of the Krebs cycle) to some visitors in the early 80s, just before he died. They thought that he had died in the previous century! Or the example of a famous clinical pharmacologist boasting that it was his discipline's 16th birthday.

You will feel, with some justification, that there should have been more of an attempt to balance the problems with the successes, not just in therapy, but in process. How much better would have been a discussion of the failures of clinical trials and the subsequent development in their regulation and monitoring. What an opportunity lost, to explore the benign tyranny of regulatory bodies like the FDA over what gets done in clinical trials. How about a debate over individual patient response and the absolute requirement for "me-too" medicines, rather than thoughtless dismissal?

All this will pass through your mind in the early part of the book. Indeed, such will be their intensity that you will consider discarding it, or putting it down for another day that never comes. Don't: complete it at a single sitting.

The first two thirds, you see, serve as a form of quality control, which is about discovering how bad things are. Looked at in that light, the authors are surprisingly humble. There is much more that could be said about how bad things have been and are now. There is much to be raged at. The final third is where the payback comes, all about making things better. Of course, they can't say everything about making research better in this one slim volume. For example, we know that clinical research in the UK is dying on its feet, a situation as bad or even worse than that portrayed in a recent Lancet editorial [1].

The authors want to have more public and patient participation in clinical research, and provide a number of interesting examples where this has happened. And where it has, it has led to better research, with more relevant outcomes, better language, and greater participation by patients themselves who become not only involved but also informed. They have a blueprint, the key points of which are:

1 Encourage honesty when there are uncertainties about the effects of treatments
2 Confront double standards on consent to treatment offered within and outside clinical trials
3 Increase knowledge about how to judge whether claims about treatment effects are trustworthy
4 Increase the capacity for preparing, maintaining, and disseminating systematic reviews of research evidence about the effects of treatments
5 Tackle scientific misconduct and conflicts of interest within the clinical research community
6 Require industry to provide better, more complete, and more relevant evidence about the effects of treatment
7 Identify and prioritise research addressing questions about the effects of treatments which are deemed important by patients and clinicians

It is probable that even writing down these points will make some people cross. Many will ask whether that's all there is? They will point to the fact that anyone trying to get research funds under point 7 is almost certainly doomed to failure. And who pays for all this? Not industry, because it's not their problem. Not government, because it is stupid. Perhaps, on a good day, downhill, and with a following wind, we might get a nibble from a small charity, but they really want cures, which means test tubes.

None of which matters. Or rather, it does matter, but it's not the point, which is that there are better ways of doing things than we sometimes do them now, and if it is possible to do things better, we should try to do it.

Many of you will hate this book, and the more you know about clinical research, the more you are likely to hate it. The more you are likely to hate it the more you should read it. It will stir you up, which is what, perhaps, the authors intended. For this reader, job done. Let's have some more polemics about the practical and funding problems of clinical research, how important it is, and what is being lost.

Reference:

1 PM Rothwell. Funding for practice-oriented clinical research. Lancet 2006 368: 262-266

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